REMARKS

Status of the Claims

Claim 1 is amended herein to recite that the liquid pharmaceutical composition comprises levocetirizine or a pharmaceutically acceptable salt thereof and a preservative mixture consisting essentially of a mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate in a ratio of 9/1 expressed in weight, said mixture being present in an amount of more than 0 and less than 1.125 mg/ml of the composition, and that the composition is substantially free of bacteria. This amendment is intended to indicate that no operative quantities of any other preservative components or antibiotic ingredients are present in the composition. Previously withdrawn claims 7-9, which recited the presence of other preservative components, are hereby cancelled. Previously withdrawn claim 10, which recited that the active ingredient is cetirizene, is hereby cancelled.

If the present amendments are found to place claims 1, 2, 5, 12, 14, 15, 17 and 27 in condition for allowance, then the Examiner is authorized to cancel without prejudice previously withdrawn method claims 18-26 by Examiner's amendment, Applicants expressly reserving the right to pursue the subject matter of those claims in one or more continuing or divisional applications.

Supplemental IDS

The corresponding European application is the subject of an Opposition proceeding commenced June 29, 2010. On September 3, 2010, Applicants herein submitted an Information Disclosure Statement citing the references that had been cited in that Opposition. The Opponent had not included a complete copy of reference D3. Applicants herein have since obtained a complete copy, and cited it to the EPO. That more complete copy of the previously cited reference is now submitted herewith with a Supplemental Information Disclosure Statement. As this is simply a more complete copy of a reference that was submitted within the three-month period after being cited in a foreign proceeding, it is respectfully submitted that no additional fee is required for submitting that complete copy now. In any event, the Office is authorized to

charge to Deposit Account 13-2490 any fee that may be deemed to be owed in connection with the submission of this Supplemental IDS.

Rejection of claims 1-2, 5, 12, 17 and 27 under 35 USC 103

Claims 1-2, 5, 12, and 17 stand rejected as obvious over DeLongueville et al. (WO 02/47689 A2), Gilliland 1 (1992; J. Appl. Bacteriol.; 72: 252-57); and Gilliland 2 (1992; J. Appl. Bacteriol.; 72:258-61) and Doron et al. P2001 Int'l J. Antimicrobial Agents 18: 575-578) in view of Routledge (1998; Toxicol. Appl. Pharmacol.; 153:12-19). In light of the foregoing amendments, this rejection is respectfully traversed.

The present invention is based on the surprising finding that the active substances belonging to the family of substituted piperazines, such as levocetirizine, possess a preservative effect in aqueous solutions (specification, page 2, lines 4-6), thereby enabling use of lesser amounts of preservatives, such as parabens. Thus, applicants herein have made the unexpected finding that a pharmaceutical composition comprising such an active substance and a reduced amount of preservatives is stable (i.e., resistant to microbial contamination) for a long period of time. (Id., lines 11-15) Accordingly, independent claim 1 as amended is directed to a composition comprising levocetirizine and a preservative mixture consisting essentially of methyl parahydroxybenzoate and propyl parahydroxybenzoate in a ratio of 9/1 by weight, said mixture being present in an amount of more than 0 and less than 1.125 mg/ml of the composition. That such a low amount of parabens without additional preservatives in a liquid pharmaceutical composition comprising levocetirizine would be sufficiently antimicrobial was unpredictable from the prior art.

It is significant that the present invention is directed to a liquid *pharmaceutical* composition. Depending on the packaging of the composition and the intended pharmaceutical use, such compositions can come into repeated contact with dosing implements that can introduce bacteria. For example, solutions for oral consumption can be packaged in a bottle that can come in repeated contact with a dosing spoon; solutions of eye drops or nose drops will come into repeated contact with a dropper device. Such spoons and droppers can be carriers of bacteria that can then be transferred to the pharmaceutical composition. Thus, it is necessary that the liquid pharmaceutical composition remain free of bacterial contaminants not only up to the time of initial use, but also after the seal on the packaging is opened. Further, such an opened

package must remain free of bacteria over the useful shelf life of the product. (Specification, page 1, line 27 – page 2, line 3) It has been surprisingly found that the composition of the present invention can accomplish this result due to the heretofore unappreciated preservative nature of the levocetirizine itself. This result is even more surprising when one considers that other liquid pharmaceutical compositions use significantly greater amounts of preservatives, as shown by the references submitted with the response of May 4, 2010. Contrary to the Examiner, this argument does not "ignore the teachings of the record." (Action, page 4, line 1) These additional references add to the record, and provide evidence as to what those skilled in the art of pharmaceutical compositions understand to be necessary levels of preservatives.

The Doron reference teaches ratios of MP:PP approaching those recited in the present claims, but at much higher concentration levels than are used in the present invention. Doron relates to an oral rinse solution intended to destroy streptococcus bacteria on oral surfaces. It does not relate to the issues of repeated contact of a dosing implement that can introduce bacteria to the solution, nor does it address the issue of planktonic (non-immobilized) bacteria. The findings of Doron as to preservative levels and ratios effective in an oral rinse against immobilized bacteria do not teach one skilled in the art about preservative levels and ratios effective to maintain an opened pharmaceutical composition free of planktonic bacteria, where that pharmaceutical composition may be subject to repeated contact with dosing implements.

Doron does not teach or suggest that the presently claimed upper limit of 1.125 mg/g total parbens can be effective against planktonic bacteria. It is the claim as a whole that must be considered in the obviousness determination, not whether individual limitations are suggested in the prior art; it is meaningless to consider only the MP:PP ratio as taught in Doron without also considering the overall concentration of preservatives. And the Action recognizes at page 6, lines 1-7 that the data in Fig. 2 of Doron, while showing the same trend for planktonic bacteria as the data in Fig. 1 shows for immobilized bacteria, does not show the same level of anti-bacterial activity as the claimed composition. The Action refers to the data point in Fig. 2 of Doron using 0.125% MP and 0.03% PP, for a total parabens content of 0.155%, or 1.55 mg/ml. This is 37% greater than the maximum of 1.125 mg/ml of the present claims. The fact that the data is Figure 2 demonstrates zero planktonic bacteria growth at the highest MP/PP ratio does not suggest that the substantially lower amount of parabens in the claimed composition is obvious. Rather, that data in Fig. 2 of Doron et al. teaches away form the claimed invention by teaching that greater

amounts of parabens are necessary to achieve zero bacteria growth for a liquid pharmaceutical composition.

Guillard 2 was a study to determine if the effects of MP and PP are synergistic. In these studies, the amount of MP was either 0.12 or 0.14 w/v%, and the amount of PP was either 0.012 or 0.140 w/v%. Thus, the lowest amount of total preservative used was 0.12 + 0.012 = 0.132 w/v%; assuming 1 g/ml of solution, this corresponds to a total *minimum* preservative level of 1.320 mg/ml. This is 17% greater than the 1.125 mg/g *maximum* preservative level recited in the present claims. Moreover, Guillard found that this lowest dosage level did not destroy E.coli, as shown in Fig. 5 at the curve for "L methyl + L propyl." Yet the present invention has shown that a *maximum* dosage level significantly lower than Guillard's *lowest* (and ineffective) dosage level is effective as a preservative for a levocetirizine solution, due to the surprising and heretofore unappreciated preservative effects of the levocetirizne itself.

The statement spanning pages 4-5 of the Action that "With respect to the *amounts*, the use of lower amounts of a 9/1 ratio is suggested by the largest antimicrobial activity taught by Doron taken together with the ratios of Guilland 2" is respectfully traversed. The largest antimicrobial activity achieved by Doron is at an amount of parabens 37% greater than the maximum amount presently claimed; and the minimum amount of parabens used by Guilland 2 is still 17% greater than the maximum amount presently claimed. These references, taken alone or in combination, do not teach or suggest the amount of parabens of independent claim 1.

Nor do these references suggest that the presence of levocetirizene would contribute a preservative effect. The Action states at page 5, "This [greater microbial efficiency at higher ratios of MP/PP] permits less of the combination to be use to still achieve the *same* of level of antimicrobial activity in a solution. This benefit would have been expected for a combination with a drug, also." (emphasis added) Even if this unsupported statement were true, the invention herein does not lie in achieving the *same* level of antimicrobial activity, the invention lies in achieving *greater* levels of antimicrobial activity at the recited concentration and MP;PP ratios, due to the presence in the solution of a particular drug, namely, levocetirizene.

To the extent that the Action relies on the showing of "some antimicrobial activity," (Action page 7) the claims have been amended to recite that the pharmaceutical compositions of the present invention are "substantially free of bacteria," such that Doron and Guillard 2 which establish "some" antimicrobial activity do not render the claimed invention obvious.

The Action states at page 8 that there is no limitation in the claim regarding resistance to bacteria. Claim 1 has been amended to recite that the claimed composition is substantially free of bacteria.

The Action states at pages 9-10 that the claims are written in an open form that allows the presence of other antimicrobial agents. Claim 1 has been amended so that the only preservative components are methyl paraben and propyl paraben, in the ratio and total amounts recited in the claim.

As all bases of rejection have been addressed by the foregoing amendments, a Notice of Allowance is requested.

If there are any questions or comments regarding this application, the Examiner is encouraged to contact the undersigned in order to expedite prosecution.

Respectfully submitted,

Date: September 21, 2010

/Sandra B. Weiss/
Sandra B. Weiss
Registration No. 30,814

McDonnell Boehnen Hulbert & Berghoff LLP
300 South Wacker Drive
Chicago, IL 60606

Telephone: 312-913-0001
Facsimile: 312-913-0002